

A worsening problem in ALS: insurance barriers between drug approvals and patient access

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For most of the past 150 years, clinicians have had few treatments to offer patients with ALS. Riluzole was approved in 1995,¹ and this ushered in an era initially characterized by hope for the rapid development of new therapeutics. However, despite great progress in the development of disease models, breakthroughs in understanding ALS pathophysiology, and large federal and pharma investment, more than 20 years elapsed before the next positive phase 3 trial.^{2,3}

In the past six years, three new drugs have been FDA-approved for ALS: edaravone (an antioxidant that slows accumulation of disability by about 30% over 6 months),³ sodium phenylbutyrate/taurursodiol (a combination with multiple intracellular actions which similarly slows disability and also prolongs survival by 4–6 months)⁴ and tofersen (an antisense oligonucleotide which lowers mutant SOD1 protein and neurofilament light chain levels).⁵ This progress is much welcomed, but it has led to a worsening problem in ALS: insurance barriers between drug approvals and patient access. The most extreme examples are payors who deny coverage for newer FDA-approved medications, claiming they are “experimental” (ex. 6). Other payors have instituted “step therapy”⁷ and are only covering the newer medications for those who “fail” riluzole.⁸ Some only cover the newer medications for patients who meet certain clinical criteria, similar to the entry criteria for the pivotal trials.^{8–11} In our experience, these insurance barriers are resulting in already-stretched clinicians and clinic staff needing to spend time on prior authorization forms, appeals of denials, and peer-to-peer reviews. More importantly, all of this results in potentially harmful delays between a medication being prescribed and a patient being able to start taking it.

To better quantify and understand the impact of these insurance barriers across more providers and clinics, we conducted and herein report the results of a survey of our colleagues in the Northeast ALS Consortium (NEALS).

We created a 16-question survey to better understand ALS Clinician perspectives on the barriers associated with riluzole, edaravone, and sodium phenylbutyrate/taurursodiol treatments (Figure 1). We did not include tofersen because it was not FDA-approved at the time our

survey launched. An electronic link to the survey was sent to 128 clinicians identified as primary site investigators in the Northeast ALS Consortium (NEALS). The link was sent three times between May 14 and May 30, 2023.

Twenty-eight clinicians completed the survey, for a response rate of 22%. The average number of patients with ALS being followed by the respondents was 168.

Clinicians were asked about the percentage of patients they felt *should be* taking each of the 3 drugs, versus the percentage that *are* taking it (Table 1). There was a large amount of variability in responses between different clinicians. The gap between these estimates for riluzole was 10%; it was 19% for edaravone and 38% for sodium phenylbutyrate/taurursodiol.

Clinicians were asked to rank the barriers to getting more patients on each drug, from biggest (1) to smallest (4, Table 2). For riluzole, the biggest barrier was a lack of patient interest. For edaravone and sodium phenylbutyrate/taurursodiol, the biggest barrier was payor restrictions.

Clinicians were asked about the percentage of prescriptions on which they encountered a need for prior authorization, denials with options to appeal, and final insurance denials (Table 3). All of these barriers were rare with riluzole. Denials with options to appeal occurred with more than half the prescriptions for edaravone and for sodium phenylbutyrate/taurursodiol. Less than 1% of riluzole prescriptions were met with a final insurance denial, while more than 25% of those for the newer medications met this fate. Given the frequency of these insurance barriers, it is not surprising that the average clinician time per script for riluzole was only 7 minutes, but it was more than 100 minutes for the newer medications. The delay between the script being written and patients being able to access the drug averaged only 4 days for riluzole, but it was around a month for edaravone or sodium phenylbutyrate/taurursodiol. Although not universal, clinicians felt on average that the delays between scripts for sodium phenylbutyrate/taurursodiol and access were more than 50% likely causing patients harm (Figure 2).

Our small survey confirms our impressions across a wider sample of clinicians. Insurance barriers, while not the only reasons, are the *main* reasons for the large gaps between the percentage of patients with ALS who *should be* taking edaravone and sodium phenylbutyrate/taurursodiol versus the percentage that *are* taking these. Prior authorizations and appeals of denials are commonly encountered in the prescribing of the newer ALS medications; these cause significant time burdens for physicians and delays between script and patient access. At least in the case of sodium phenylbutyrate/taurursodiol, these delays are perceived by experts as more than 50% likely harmful to patients. This perception is supported by open-label extension data showing that patients who receive sodium phenylbutyrate/taurursodiol early do much better on functional measures, risk of hospitalization, and survival compared to those who receive it after a delay.^{12,13}

There are limitations to this study. First, we did not address the pricing of the newer ALS medicines, which, given the small effect sizes and lack of replication trials for edaravone and sodium phenylbutyrate/taurursodiol, some have understandably criticized.^{14,15} Determining how many ALS trials or what effect size is needed to establish confidence in an ALS drug, or to determine its cost, are beyond the scope of this paper. We refer readers to an excellent editorial that touches on some of these complex questions.¹⁶ Second, we did not survey payors nor patients to get their perspectives. Finally, the response rate of our survey was low, which may have introduced bias. Nonetheless, we believe we have identified an important and worsening problem facing ALS clinicians.

These types of insurance barriers are not unique to ALS treatments,^{7,8} but they are especially problematic due to the aggressive and fatal nature of the disease. And they are not evidence-based. FDA-approved therapies are not “experimental.” The idea of a patient needing to “fail” riluzole is farcical since essentially all ALS patients will worsen over time. Using clinical trial inclusion criteria as a basis for coverage reflects misunderstanding both of the differences between clinical trial methodology and clinical care, as well lack of understanding of the nature of ALS. Clinical trials attempt to reach efficacy conclusions as efficiently as possible, while practice entails treating as many patients as effectively as possible. The idea that a clinical trial population in ALS is somehow etiologically different than those needing care is not supported by any available data. Indeed, at this time, the authors of this paper do not believe there is a point in ALS progression where the available drugs would no longer be effective. Roadblocks to the use of effective drugs in combination with riluzole mean that patients get access either late or not at all. As ALS involves the inexorable death of motor neurons, delaying treatment is a guarantee of inadequate treatment.

For other diseases, advocacy has been effective in reducing insurance barriers.¹⁷ Laws have even been enacted to ensure insurance coverage for treatments that experts felt were important.^{8,17,18} We hope that discussion of this important topic will result in recognition from payors that ALS patients deserve access to care that meaningfully impacts their disease. If not, then perhaps it will galvanize advocates and lawmakers toward addressing the unacceptable insurance barriers to newer ALS treatments. People affected by this disease have waited long enough for these treatments.

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Table 1. Based upon what you know today about these drugs, what percentage of the people with ALS that you care for should be/are taking:

	Riluzole	Edaravone	NaPB/TURSO
<u>Should Be Taking</u>	88% (0, 100)	51% (0, 100)	76% (0, 100)
<u>Are Taking</u>	78% (30, 98)	32% (5, 95)	38% (5, 90)
<u>Difference in Means</u>	10%	19%	38%

Data presented are means and (ranges).

Table 2. Rank the barriers to getting more patients on each drug, from biggest (1) to smallest (4):

	Riluzole	Edaravone	NaPB/TURSO
Lack of physician confidence in benefits	1.9 (0.88)	2 (0.82)	2.6 (0.79)
Lack of physician confidence in safety	3.1 (0.65)	3.8 (0.52)	3.1 (0.88)
Lack of patient interest	1.7 (0.98)	2.8 (0.84)	3.1 (0.94)
Payor restrictions	3.3 (1.0)	1.5 (0.74)	1.2 (0.69)

Data presented are means (and standard deviations)

Table 3. On what percentage of prescriptions do you encounter the following:

	Riluzole	Edaravone	NaPB/TURSO
Prior Authorization	20.7% (36.4)	87.2% (9.7)	90.3% (9.7)
Insurance Denial with Option to Appeal	5.6% (3.3)	56.2% (22.1)	65.2% (26.5)
Final Insurance Denial	0.3% (0.42)	26.1% (20.4)	28.8% (17.1)

Data presented are means (and standard deviations)

Table 4. Time To Get Each Drug

	Riluzole	Edaravone	NaPB/TURSO
Clinician Time Per Script	7 minutes (0, 30)	110 minutes (15, 360)	126 minutes (15, 360)
Delay Between Script and Patient Access	4 days (0, 30)	29 days (5, 60)	32 days (2, 60)

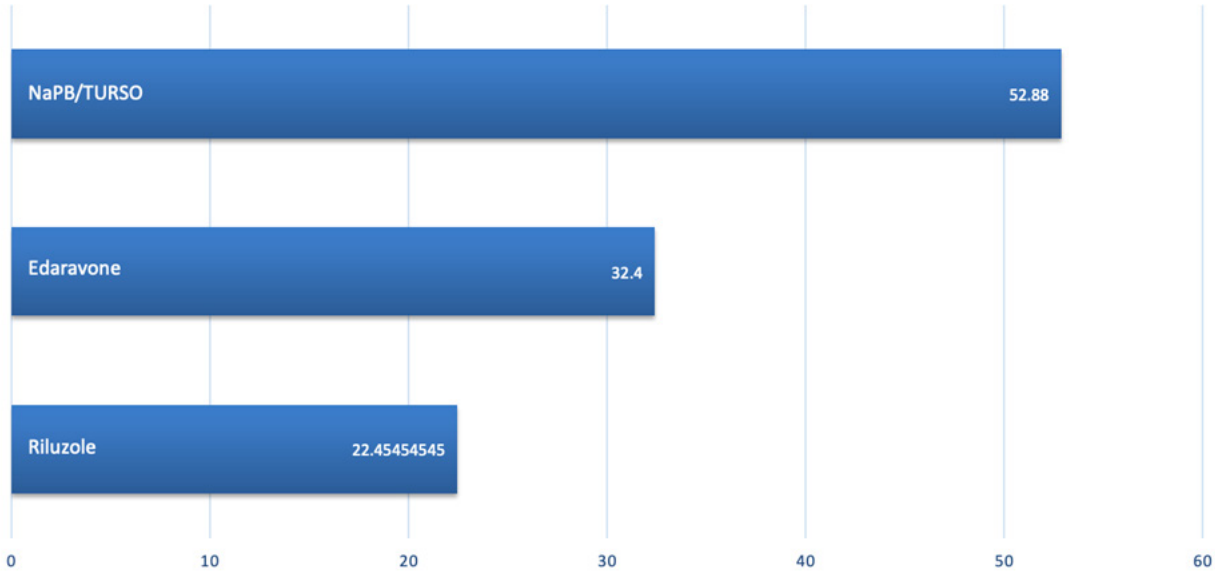
Data presented are means and (ranges).

Figure 1. Survey Questions

1. Based upon what you know today about these drugs, what percentage of the people with ALS that you care for should be taking riluzole, edaravone, sodium phenylbutyrate/taurursodiol?
2. In your estimation, what percentage of the patients you care for are currently taking riluzole, edaravone, sodium phenylbutyrate/taurursodiol.?
3. Rank the barriers to getting more patients on riluzole from biggest (at the top) to smallest (at the bottom):
 - a. Lack of physician confidence in benefits
 - b. Lack of physician confidence in safety
 - c. Lack of patient interest
 - d. Payor restrictions
4. Rank the barriers to getting more patients on edaravone from biggest (at the top) to smallest (at the bottom):
 - a. Lack of physician confidence in benefits
 - b. Lack of physician confidence in safety
 - c. Lack of patient interest
 - d. Payor restrictions
5. Rank the barriers to getting more patients on sodium phenylbutyrate/taurursodiol from biggest (at the top) to smallest (at the bottom):
 - a. Lack of physician confidence in benefits
 - b. Lack of physician confidence in safety
 - c. Lack of patient interest
 - d. Payor restrictions
6. On what percentage of riluzole prescriptions to you encounter the following:
 - a. Prior authorization
 - b. Insurance denial with option to appeal
 - c. Final insurance denial
7. On what percentage of edaravone prescriptions to you encounter the following:
 - a. Prior authorization
 - b. Insurance denial with option to appeal
 - c. Final insurance denial
8. On what percentage of sodium phenylbutyrate/taurursodiol prescriptions to you encounter the following:
 - a. Prior authorization
 - b. Insurance denial with option to appeal
 - c. Final insurance denial
9. How much effort (in average minutes per prescription) does it take your team to get a patient on:
 - a. Riluzole
 - b. Edaravone
 - c. Sodium phenylbutyrate/taurursodiol.
10. How much time passes (in average days) between your prescription for riluzole and your patient getting it from their pharmacy?
11. How much time passes (in average days) between your prescription for edaravone and your patient getting it from their pharmacy?
12. How much time passes (in average days) between your prescription for sodium phenylbutyrate/taurursodiol and your patient getting it from their pharmacy?
13. On a scale from 0 (not at all) to 100 (very), how confident are you that delays in starting riluzole are harmful to your patients?
14. On a scale from 0 (not at all) to 100 (very), how confident are you that delays in starting edaravone are harmful to your patients?
15. On a scale from 0 (not at all) to 100 (very), how confident are you that delays in starting sodium phenylbutyrate/taurursodiol are harmful to your patients?
16. How many people with ALS do you currently provide care for?

Figure 2. Clinician Confidence in Delays Causing Harm

On a scale of 0 (not at all) to 100 (very high), how confident are you that delays in starting these medications are harmful to your patients?



Data presented are means. Standard deviations: Riluzole (30.6), Edaravone (28.1), NaPB/TURSO (32.2)